Edited by
Kenneth S. Warren
and
Elizabeth F. Purcell

THE CURRENT STATUS AND FUTURE OF PARASITOLOGY

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THE FUTURE OF PARASITOLOGY: AN OVERVIEW

Joshua Lederberg

None of my published research has been on organisms customarily called parasites. Nor is my assigned subject, "The Future of Parasitology," one that is enhanced by laboratory data. I will offer some general observations and contrast them with general wisdom on how health research is conducted. The concerted scientific attack on communicable diseases is an appropriate precedent for the problems we now address in parasitology.

The discovery in the late 1800s of bacteria as agents of disease was a revolutionary advance, albeit not a scientific revolution in T. S. Kuhn's sense. It may be the best example to date of a scientific insight becoming a reductionist foundation for practical advances of the most sweeping and important kind.

The germ theory, and the basic techniques for the recognition and isolation of various species of pathogenic microorganisms in pure culture established by Louis Pasteur, Robert Koch, and Ferdinand Cohn, gave us a sweeping scientific principle looking for the appropriate questions to which it would be a solution. As far as I am aware this principle has had more important consequences for the improvement of public health than any other concept in the history of mankind. But today we are uneasy because we cannot so easily replicate that kind of comprehensive advance for our remaining health problems such as heart disease, cancer, and schizophrenia.

The miracle drugs—the antibiotics—are the most recent and potent example of the application of these elementary principles to health problems. Nothing since has so profoundly captured the public's imagination for the justification of health research over the last twenty-five to thirty years.

The result has been increasing tension between the ultimately well-founded expectations of public constituencies, who considered our advances in infectious bacterial diseases as a prototype of the fruit of investments in health research, and the realization that we do not yet have principles of comparable power and immediate relevance to many other afflictions with which we are now concerned.

Important work has been going ahead steadily, but compared to the revolutionary advances of the first part of this century it seems to be progressing in a painfully slow fashion. At the same time we have witnessed exponential increases in government investments in health research, and the disparity between anticipated scientific discoveries and the level of funding is brought forcefully to our attention in every budget cycle of the Congress.

The introduction of the germ theory of disease led to a rapid penetration of one large set of public health problems. I hold the view that it is precisely in parasitic infection that we have the nearest analogue to that kind of opportunity. My major premise is that when our understanding of the eukaryotic agents of infection can be brought to a comparable level of depth and insight—complicated by the facts that parasites are indeed eukaryons, often intracellular in habitat, and resemble the metabolism of the host more closely than do bacterial parasites—we will see advances as sudden and as spectacular as were achieved for most of the bacterial infections.

There are of course many problems. On the social and political side is the fact that the United States is no longer a colonial and imperial power of the style that had strong motivation to find cures for diseases that wreaked havoc in tropical countries. While promoting decolonization we have shamefully neglected our human responsibility to allocate resources to help solve the health problems of the developing world, for they are not at the forefront of concern in the health statistics of our

country. But even that probably unduly minimizes the impact parasitic infection will continue to have, even on the health of our own citizens and livestock.

The assemblage of scientists at this conference is testimony to the capacity to mobilize a diverse set of experiences and intellectual resources. If the material resources could be made available, with the kind of nucleation represented here, very rapid progress, a veritable new wave of research, would at this point be inevitable.

But the political obstacle is serious, and I do not understand why it is so difficult to get a broader range of public support for the kinds of questions with which we are mutually concerned. Perhaps we still have not transmitted even the bare factual message that malaria remains the world's most important disease in terms of its impact on the health, welfare, and economic and social development of vast numbers of people.

We must further not overlook the fact that even while the management of bacterial infectious disease is a paragon, our self-congratulation must be tempered, for we have by no means dealt with all the health problems in this country. We will probably see even more of them in the future, with the continued and recurrent emergence of antibiotic-resistant strains of microorganisms and, quite possibly, with the emergence of new diseases and infections caused by other aspects of the continuing evolution of that huge part of the biosphere reflected by the microbial world.

In a way, I consider our present management of bacterial infections, particularly tuberculosis and leprosy, a disgraceful testimony to the inadequacies of our scientific base. In part this is a reflection of the insufficient penetration of available scientific methodology in this field. I may be wrong, but I believe it is barbarous that we continue to use an agent such as BCG vaccine for large-scale tuberculosis immunization campaigns at a time when there is much more we should know about the biology of the organisms used in BCG. We should go much more deeply into the question of how to purify the components so we may have a choice of strains, mechanisms of pathogenesis, and so on.

Fiascos such as the one in India, as revealed in a recent World Health Organization study, are inevitable if we are to go

back over sixty years for material that has not been examined from any modern, sophisticated scientific standpoint.

As for leprosy, a far more effective line of investigation could be conducted with genetic analysis of the infection. We face the serious question of how to deal with an organism that is so peculiar in its range of susceptible species. I do not know of any other area of biology that links the armadillo and the human.

To deal with either leprosy or tuberculosis requires a deeper knowledge of the behavior of our cellular defense mechanisms than we have at the present time. Getting the organisms into pure culture is only the starting point of effective science. As soon as we get that deep into human physiology we are dealing with paradigms of investigation far more intricate and difficult than, for example, growing a diphtheria organism in a test tube and finding it produces an exotoxin that will kill guinea pigs in trace amounts. It is of course no accident that, from a world public health perspective, these bacterial infections are intractable residues that bear an interesting resemblance to the parasitoses.

There is likely to be needless tension between the perspective of the experimental, laboratory-oriented investigator, on the one hand, who thinks of parasitology as an exciting, challenging playground for linking biology, life cycle, microbiology, cell biology, and developmental aspects of a fascinating group of organisms—which, by the way, happen to have public health implications—and, on the other hand, that of the sanitary, public health-oriented researcher who quite correctly points out that major advances in public health throughout the world depend far more on environmental management, sanitation, and interrupting the ecological patterns of our parasitic life cycle than on specific therapeutic measures and interventions of human physiology.

Both perspectives are absolutely indispensable for further progress in the field because, even with a global public health orientation, the vastness of the stakes is matched only by the vastness of the errors that can be made when programs are mounted without an adequate base of biological insights as to the nature and behavior of the relevant organisms—whether at the ecological or molecular level.

The concept that it is possible to eradicate almost any known disease is a treacherous one, although smallpox is an example of a disease with very special peculiarities that made it most amenable to eradication. We should keep our fingers crossed, however, because we do not know enough about the genetics and the evolution of that particular virus or its affinities with other viruses of the world. Nor do we know enough about the molecular biology of the virology of smallpox, compared to other related viruses, to be certain that outbreaks will not recur. One should be wary about the prospect of the development of a global herd that twenty or thirty years from now will not have been immunized against smallpox.

The possibility of the reevolution of the smallpox virus must be matched against the de novo emergence of a wide range of other viruses, events of perhaps comparable likelihood.

It is a matter of general concern that, as we strive for a sanitary world, we are also developing a large sensitive herd! We are, then, scarcely giving enough thought to the revolutionary biological reengineering of our own species, which is implicit in effective sanitation. Never before in our history have we had such large numbers of individuals whose immunological experiences and contacts with infectious agents have been so drastically altered because of the very success of the measures we are hoping to introduce. I have no idea what the further implications of that reengineering will be, but I do not see how it can fail to penetrate other aspects of the life cycle of the human organism in ways that will not always be what we hope for.

The question of large-scale control of any species through sanitary measures—be they vectors or parasites—cannot be undertaken thoughtfully without much deeper inquiry into the biology of the target organisms, and particularly of their capacity for future evolution.

We must be concerned about other animal hosts for the parasite and about the possibility that virulent mutants or hybrids may reemerge from the gene pool of related species. For this we already have the example of pandemic influenza, which is believed to come from viruses normally resident in birds.

Certainly those measures used in environmental control should in some way bypass the logistical problems that would be involved, for example, in providing recurrent chemotherapy to large numbers of individuals, particularly in areas of the world with poor economic conditions, inadequate transportation, and limited medical services. We have to find solutions where they happen to be, not where we would like them to be.

In the first instance, the new inputs from molecular and cell biology have their most obvious application in the identification of purified antigenic components. The possibility of dissecting the malarial plasmodium to find those antigenic constituents that can be used most effectively for vaccination is of course a very exciting challenge, and it is gratifying to see how rapidly William Trager's work in this field is being taken up in many laboratories that are investigating malaria.

That is the most obvious application and it was waiting in the wings for a technological breakthrough with which to exploit it. I hope this does not obscure a variety of other ways in which that type of experimental biological insight can be made indispensable. I call particular attention to the virtues of live vaccines. It should be possible to prepare them for any organism about which we have an intimate knowledge of its life cycle and control of its genetics.

When Louis Pasteur produced a rabies vaccine, without being aware of it he was selecting for less virulent strains because they have a lower neurotropism. We know very little today about the molecular basis of the altered strains or how the procedure used for cultivating them resulted in selection for less virulent mutants. Alfred Sabin was working equally in the dark when he developed live poliomyelitis vaccine. Even without knowing the fundamental biology one can proceed in a certain way if one has the technology to handle the organism.

But potential hazards lurk deep in both these situations precisely to the extent that we are not able to foresee what genetic interactions are still possible for those organisms. And of course the fact that we still need vaccinations for poliomyelitis means we have some residual problem with that disease. By that criterion the situation is far from perfect.

Perhaps even more important, the cell biology of the parasites could be considered in terms of understanding their development. They are, after all, eukaryotes that go through interesting and important developmental cycles. It is precisely those cycles that will show us targets of application for interventions that will drive a wedge between their developmental controls and metabolism and our own, because so much of what they do will arise from our common phylogenetic origins and the mutual adaptations of a parasite that has been living intimately in our bodies.

The fundamental perspective for any rational development of chemotherapeutic drugs merges very closely with that of pesticides, for the key to the control of both pests and parasites is an understanding of singularities of their developmental behavior compared to host and crop.

Another arena that tends to be put aside—and this is one of the tragedies of public health science in many areas where the most cogent intersection between the experimental laboratory and the public health perspective is needed—are "side effects." I cannot think of a more insidious expression for a set of phenomena that, far from being side effects, increasingly dominates our central policy concerns about the provision of agents to large populations.

Mention of the drug hycanthone gives some notion of what I am referring to. Many such controversies are impossible to resolve at the present stage of our knowledge of comparative toxology, of how to extrapolate data obtained under controlled laboratory conditions—and therefore perforce on a limited sample of individuals, ideally nonhumans—to what the risk will be when large populations are exposed.

Today, particularly, when questions of source, on the one hand, and target, on the other, of health research raise so many political problems, there is so much latent distrust that the potential magnitude of the so-called side effects dominates the situation more and more.

Side effects should very nearly occupy center stage in an examination of any program of practical intervention, rather than be left to the last minute as a kind of mop-up activity when the question is raised of whether untoward effects have been observed in an epidemiological survey, or when a laboratory

animal is found to exhibit an unexpected side effect. The issue for physiologically potent chemicals is not whether they will have "side effects," but the details of potency, morbidity, and relationship of risks to benefits.

Any agent distributed to a great many individuals, under the inevitably poorly controlled conditions of a public health program, is bound to elicit some kind of imputed hazard. How can one be forearmed against this in ways that enable a rational examination of whether the danger is real or not? That is something that needs to be brought into our studies at the earliest stage. Simple empirical history tells us that, unfailingly, such accusations will be motivated and will be lodged against any agent introduced under those circumstances.

Finally, some reflections on medical progress in other fields that may bear some relationship to what we hope may result from this conference.

All of us who strive for a rational model of the universe we are exploring, and who work hard to improve the underpinnings, biological understanding, and chemical explanation of phenomena under study, believe that in the long run the use of basic science for health improvement is the most important route.

The problem is that things hardly ever work that way. If one examines the history of discoveries in the health field one finds no more than a minor sprinkling of circumstances where the framework of biological theory in any depth preceded our understanding of how to approach a particular disease.

The outstanding exceptions to that rule are the discoveries of Pasteur and Koch. They had their own prehistories of initial discoveries of bacterial agents of specific diseases. That territory having been opened up, in a few cases there was a crude theoretical framework for further exploration. But if we go back to 1830 instead of 1880, in terms of examining the history of that phenomenon, it falls within the paradigm I am about to express.

Almost every important advance in health practice, and in science generally, has emerged through Pasteur's paradigm, that is, "chance favors *the prepared mind.*" (I would substitute "practical observation" for "chance.") That principle may be

described as the natural history of what one sees in the test tube, at the bedside, in the field, or in public health observations of a disease: the confrontation with real problems; contradictions of one's theoretical expectations; insights about directions to take; essentially empirical discovery in the initial instance. Without immersion in a rather broad way in the complex system we are trying to deal with we simply will not have the encounters to provide the answers.

Those insights, those hopes, will be paralyzed at the outset, however, if they are not accompanied by the most sophisticated tools for further analysis. The discrepancies in our world view may not even be recognized unless a well-constructed theoretical framework exists to begin with. Their further exploitation will not be possible without many more basic scientific fundamentals than we are able to offer at a given time.

I have begun to despair of being able in my lifetime, or in those of two or three generations of our descendants, to fulfill the reductionist dream of a biological theory that will enable us to predict the nature of disease. That has been a misconception of the way fundamental science will eventually solve all our problems. I insist that we cannot make effective progress in the exploitation of any of the wide variety of empirical findings without that very sturdy base of further insights.

For this to work, there needs to be good communication among the different elements of the system. I do not expect every laboratory investigator to be able to spend a lot of time with researchers working in the field, or vice versa. But if people who are studying the natural history of disease are not in close communication with those who understand how to do the follow-up work we will miss the most important leads, and both health and science will suffer.